Simple Spectrophotometric and HPTLC-Densitometric Methods for Determination of Cefdinir in Bulk Powder and Pharmaceuticals, and in Presence of its Hydrolytic Degradation Products

Omar Abdel-Aziz[1], Maha Farouk[1], Reham Nagi[1]*, Laila Abdel-Fattah[2]

[1]Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.
[2]Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt.

ARTICLE INFO

ABSTRACT

The present work describes development and validation of four different stability indicating methods for quantitative analysis of cefdinir (CFD) in bulk powder and pharmaceuticals, and in the presence of its acid and alkaline induced hydrolytic degradation products. The first method is based on derivative spectrophotometry. First derivative spectrophotometry was applied where CFD was determined at 313.4 nm in the presence of its alkaline degradation product and also second derivative spectrophotometry where CFD was determined at 298.2 nm in the presence of its acid degradation product. The second method is based on the first derivative of ratio spectrophotometry of CFD at 312 nm in the presence of its acid degradation product and at 310.2 nm in the presence of its alkaline degradation product. The third method is based on the mean centering of ratio spectrophotometry where the drug was determined at 288.4 and 284.8nm in laboratory prepared mixtures with its acid and alkaline degradation products, respectively. The fourth method is HPTLC-densitometry using diethylether-methanol-water-glacial acetic acid (6: 3: 1: 0.05, v/v) as a developing system. Due to simplicity, rapidity and accuracy of the proposed stability indicating methods, they are effective for quality control analysis.

INTRODUCTION

Cefdinir (CFD), third generation cephalosporin, is chemically known as [6R-[6a,7β (Z)]]-7-[[(2-amino-4-thiazolyl) hydroxyimino) acetyl] amino]-3-ethyl-8-oxo-5-Thia-1-azabicyclo-(4.2.0.)-oct-2-one-2-carboxylic acid (Merck, 1996). Of several oral cephalosporins, CFD is recommended as an alternative therapy for children with acute otitis media who have type 1 hypersensitivity to betalactamse (Bowlware et al, 2006). It is usually a well-tolerated antibiotic, with most adverse effects being mild and self-limiting (Perry et al, 2004; Arguedas, 2006). CFD contains a β-lactam ring which is very labile to acid and base (Helaleh and Abu-Nameh, 1998; El-Obeid et al, 1999) making it very important to develop specific methods for estimation of this drug in presence of possible degradation products. Detailed survey of literature of CFD revealed several methods for

its determination in pharmaceutical formulations and biological matrices like, spectrophotometry (Shah and Pundarikakshudu, 2006; Singh et al, 2010), polarographic technique (Rajeev et al, 2007), HPLC (Hadad et al, 2009; Khan et al, 2011), and LC/MS/MS methods (Chen, 2006). However, most of these analytical methods do not appear to have widespread utility, especially at the industrial level, where simple, cost-effective, and specific methods are needed. Moreover, far to our present knowledge, no stability indicating spectrophotometric nor HPTLC methods has been published in the literature. Therefore, we attempted to develop rapid, sensitive, accurate, and specific spectrophotometric methods (derivative, derivative ratio and mean centering of ratio spectra) and HPTLC-densitometric method for determination of cefdinir in bulk powder and oral dosage forms, and in presence of its acid and alkaline induced hydrolytic degradation products. The results were validated in accordance with International Conference on Harmonization guidelines (ICH, 2005).

* Corresponding Author
Reham Nagi, E-mail: drreham2003@gmail.com
Phone: +201151249939

MATERIALS AND METHODS

Instrumentation

- Double-beam Shimadzu (Japan) 1601 PC UV-Visible spectrophotometer connected to a computer fitted with UVPC personal spectroscopy software version 3.7 (Shimadzu).

- Desaga densitometer model CD 60 (Germany). AS 30 Desaga applicator. Desaga UV lamp with short wavelength (254nm). HPTLC plates precoated with silica gel 60 F_{254} (20.0 × 10.0 cm) from E. Merck, Germany.

Materials and reagents

CFD pure sample was obtained from (Bristol-Myers Squibb Pharmaceutical Co., Cairo, Egypt), 99.71%. CFD capsules (Novartis Pharma S.A.E, Cairo, under licence from Novartis Pharma AG., Basle, Switerland, Egypt), labelled to contain 300 mg CFD per capsule. CFD suspension (Novartis Pharma S.A.E, Cairo, under licence from Novartis Pharma AG., Basle, Switerland), labelled to contain 125 mg CFD per 5.0 mL A diluent (50 mM potassium dihydrogen phosphate, adjusted to pH 6.8 with 1 M NaOH) was used for the preparation of stock solutions of the standard and test samples. Methanol and water (HPLC grade) were purchased from (Riedel-de Häen, Sigma-Aldrich, Germany). Diethylether and glacial acetic acid were purchased from (E. Merck, Darmastadt, Germany); sodium hydroxide and hydrochloric acid (BDH).

Preparation of standard solution of cefdinir

For spectrophotometric methods, stock standard solution of CFD (1.0 mg/mL) was prepared by accurately weighing 100.0 mg of CFD into 100-mL volumetric flask, dissolved in 50 mL of the specified diluent solution and the volume was completed with it. Then, working standard solution (100 µg/mL) was prepared by transferring 10.0 mL of the stock standard solution into 100-ml volumetric flask, then volume was completed with the diluent. For HPTLC, stock standard solution of CFD (2.0 mg/mL) was prepared by accurately weighing 200.0 mg of CFD into 100-mL volumetric flask, dissolved in 50 mL of the specified diluent and the volume was completed with methanol.

Preparation of standard solutions of hydrolytic degradation products

- Stock standard solution of acid degradation products (1.0 mg/mL) was prepared by accurately weighing 50.00 mg of CFD, dissolving in 20.0 mL 1 M HCl, heating in water-bath at 80°C for 3.5 hrs, then cooling, neutralizing the media with 1 M NaOH (to give pH 7.0) and then completing volume to 50.0 mL with the diluent (for spectrophotometry) or methanol (for HPTLC).

- Stock standard solution of alkaline degradation products (1.0 mg/mL) was prepared by accurately weighing 50.00 mg of CFD, dissolving in 20.0 mL 0.5 M NaOH, heating in water-bath at 80°C for 1.5 hr, then cooling, neutralizing the media with 0.5 M HCl (to give pH 7.0) and then completing volume to 50.0 mL with the diluent (for spectrophotometry) or methanol (for HPTLC).

- Working standard solutions (100 µg/mL) of the acid- and alkaline-degradation products were prepared separately for spectrophotometry by transferring 10.0 mL of their stock standard solutions into100-mL volumetric flasks, and then volumes were completed with the diluent.

- Complete hydrolytic degradation of CFD in acid and alkaline media was confirmed by applying the proposed HPTLC method.

General Procedures

Spectrophotometric methods

- For derivative spectrophotometry, second derivative (^{2}D) was applied to the zero-order absorption spectra of CFD and its acid degradation product binary mixtures with $\Delta\lambda = 8$ nm and scaling factor 100, and CFD was determined at 298.2 nm. First derivative spectrophotometry (^{1}D) was applied to the absorption spectra of CFD and its alkaline degradation product binary mixtures with $\Delta\lambda = 8$ nm and scaling factor 10, and CFD was determined at 313.4 nm.

- For first derivative ratio spectrophotometry (^{1}DD), Zero order spectra of CFD & its acid degradation product binary mixtures were divided by the spectrum of the acid degradation product (40 µg/mL) then first derivative was applied for these ratio spectra (^{1}DD) using scaling factor 10 and $\Delta\lambda = 4$ nm. Peak amplitudes were measured at 312 nm. While Zero order spectra of CFD and its alkaline degradation product binary mixtures were divided by the spectrum of the alkaline degradation product (40 µg/mL) then first derivative was applied for these ratio spectra (^{1}DD) using scaling factor 10 and $\Delta\lambda = 4$ nm. Peak amplitudes were measured at 310.2 nm.

- For mean centering of ratio spectra, the previously obtained ratio spectra for CFD, and its acid and alkaline degradation products binary mixtures were mean centered and peak amplitudes were measured at 288.4 nm and 284.8 nm, respectively.

HPTLC-densitometric method

Analysis was performed on 20 x 10 cm HPTLC plates pre-coated with silica gel 60 F_{254} (E. Merck). The plates were spotted 2 cm apart from each other and 1cm apart from the bottom edge.

The chromatographic tank was pre-saturated with the developing system for 15 min, then the plates were developed by ascending chromatography using diethylether-methanol-water-glacial acetic acid (6: 3: 1: 0.05, v/v) as a developing system to a distance of 9.5 cm. The plates were air dried, detected under UV-lamp and then, scanned at 285 nm under the following experimental conditions of measurements: photo mode=reflectance, scan mode=linear slit scanning, slit width = 0.4mm, slit height = 0.02mm, result output= densitogram and peak list.

Method validation

Linearity

In case of spectrophotometric methods, accurately measured volumes of CFD working standard solution (100.00 µg/mL) were transferred into a series of 10-mL volumetric flasks, diluted to volume with the diluent to obtain suitable concentration range for each proposed spectrophotometric method. Zero order spectra were recorded using the diluent as blank. The previously mentioned general procedures were then followed and the values of peak amplitudes were plotted against the corresponding concentrations; the regression equations were then computed.

In HPTLC, accurately measured volumes (0.5– 6.0 mL) of CFD stock standard solution (2.0 mg/mL) were transferred into a series of 10-mL volumetric flasks, diluted to volume with methanol to obtain a concentration range of 0.10 – 1.20 mg/mL. A 5 µl volume of each solution was applied to the plates in triplicates, the chromatographic conditions were adjusted, the plates were developed and the peak areas were measured. The calibration curve representing the relationship between the integrated peak area and its corresponding concentration was constructed and the regression equation was recorded.

Accuracy

The previously mentioned procedures under linearity were repeated for determination of different concentrations of CFD. The concentrations were calculated from the regression equations and the percentage recoveries were then calculated.

Precision

Three concentrations of CFD were analyzed five times intra-daily and on five successive days using the previously mentioned procedures under linearity. The mean percentage recovery and the relative standard deviation were calculated.

Specificity

The specificity of the proposed methods was established by the analysis of laboratory mixtures, consisting of the intact drug with its acid and alkaline degradation products, in triplicate. The peak amplitudes (for spectrophotometry) and peak areas (for HPTLC) were measured and the concentrations of CFD were then calculated from the regression equations. The mean percentage recovery and the relative standard deviation were calculated.

Application to the pharmaceutical formulations

In case of capsules, the content of ten capsules were weighed, finely powdered, and mixed thoroughly. An accurately weighed amount of the powder obtained from capsules equivalent to 300 mg of CFD was transferred into a 100-mL volumetric flask containing 50 mL the specified diluent. For oral suspension, 5 mL of reconstituted suspension was accurately transferred (after vigorous shaking) into a 100-mL volumetric flask containing 50 mL of the diluent. The content of each flask was shaken well for 15 min, completed to the mark with the diluent (in case of spectrophotometry) or methanol (in case of HPTLC) and then

filtered; the first portion of the filtrate was rejected. A suitable aliquot of each solution was diluted quantitatively with the diluent (in case of spectrophotometry) or methanol (in case of HPTLC) to obtain a concentration within the linearity range. The suggested procedures stated under linearity were followed for CFD assay. For standard addition technique, known amounts of CFD were added to the drug product, the suggested procedures stated under linearity were carried out. The concentrations, the mean percentage recovery and the relative standard deviation were then calculated.

RESULTS AND DISCUSSION

Spectrophotometric methods

Derivative spectrophotometry

Acid and alkaline degradation products of CFD have absorption spectra which overlap with that of intact CFD (Figure 1). Upon examining their first derivative spectra ([1]D), the severe overlap could be resolved for CFD and its alkaline degradation product and so CFD could be determined at 313.4 nm (Figure 2). By applying second derivative spectrophotometry ([2]D), CFD could be determined at 298.2 nm, where its acid degradation product has no contribution (zero crossing) (Figure 3). Δλ was optimized to give a well resolved peak and thus high selectivity was obtained.

First derivative ratio spectrophotometry ([1]DD)

In this method, careful choice of the divisor is of great importance (Nevado, 1992; Gracia, 1995), so different concentrations of the acid and alkaline degradation products were tried as a constant divisor, the best one for each degradation product was 40.00 µg/mL as it gave the best linear response, i.e. wider linearity range, good correlation coefficient and a near zero intercept on the ordinate of the graph. The first derivative of the ratio spectra were obtained using scaling factor 10 and Δλ=8 nm, (Figures 4 and 5). Peak amplitudes at 312nm using acid degradation product spectrum as divisor and at 310.2 nm using alkaline degradation product spectrum as divisor were proportional to CFD concentration in the range of 2-30 µg/mL.

Mean centering of ratio spectra

This method eliminates the derivative steps and therefore signal-to-noise ratio is enhanced (Afkhami and bahram, 2004) and it has been applied for resolving binary and ternary mixtures in complex samples with unknown matrices (Afkhami and bahram, 2005). The mathematical explanation of the method was illustrated by Afkhami and Bahram. Beer's Lambert's law has been obeyed at 288.4 nm using acid degradation products spectrum as divisor and at 284.8nm using alkaline degradation products spectrum as divisor (Figures 6 and7). Assay validation parameters for the spectrophotometric methods are presented in Table 1. The specificity of these methods was tested by analyzing laboratory prepared mixtures (Table 2). The data obtained shows that CFD can be quantitatively determined in presence of up to 50% of its acid and alkaline degradation products.

Table. 1: Assay validation parameters of the proposed methods for the determination of cefdinir

Parameters	¹D 313.4nm	²D 298.2 nm	¹DD 312nm	¹DD 310.2nm	Mean centering of ratio spectra 288.4nm	Mean centering of ratio spectra 284.8nm	HPTLC
Linearity:							
Correlation coefficient (r)	0.9998	0.9997	0.9996	0.9998	0.9997	0.9998	0.9995
slope	0.0161	0.0078	0.0333	0.0404	0.0643	0.0928	-
Coefficient1 (b_1)[a]			-				-49.661
Coefficient2 (b_2)[a]			-				826.532
Intercept	0.0231	0.0129	0.0426	0.0399	0.0399	0.0778	-63.945
Range	6-30µg/mL	4-24µg/mL	2-30µg/mL	2-30 µg/mL	2-24µg/mL	2-26µg/mL	0.5-6µg/spot
Accuracy(mean±SD)	99.73±0.552	99.27±0.546	99.87±0.596	99.74±0.608	99.54±0.618	100.32±0.689	100.56±0.908
Precision: (mean±RSD%)							
Repeatability	100.19±0.378	99.41±0.703	100.40±0.595	100.03±0.529	100.20±0.372	100.33±0.620	99.37±1.017
Intermediate precision	99.54±0.741	100.10±0.769	99.45±0.676	100.20±0.905	100.76±0.599	100.31±0.872	99.91±1.265
Specificity: (mean±RSD%)							
In presence of acid degradate	-	99.87±0.895	100.77±0.734	-	99.99±0.820	-	100.54±1.258
In presence of alkaline degradate	100.28±1.077	-	-	100.08±0.872	-	100.49±0.802	99.54±1.023

[a]Regression equation: $A=a+b_1 C+b_2 C^2$

Table. 2: Determination of cefdinir in laboratory prepared mixtures with its acid and alkaline degradation products by the proposed spectrophotometric methods.

Degradation products µg/mL	Cefdinir µg/mL	%Recovery of cefdinir* ¹D 313.4nm	%Recovery of cefdinir* ²D 298.2nm	¹DD 312nm	¹DD 310.2nm	Mean centering of ratio spectra 288.4nm	Mean centering of ratio spectra 284.8nm
2	20	101.85	100.37	99.69	101.29	98.85	101.61
4	20	101.27	100.86	101.32	100.64	100.40	101.12
8	20	99.98	98.62	101.03	100.19	99.31	100.58
12	20	98.90	100.68	100.62	98.94	99.78	99.36
16	20	99.82	99.39	101.71	99.24	101.01	100.02
20	20	99.89	99.30	100.27	100.17	100.58	100.25
Mean ±RSD%		100.28±1.077	99.87±0.895	100.77±0.734	100.08±0.872	99.99±0.820	100.49±0.802

*Mean of three determinations

Table. 3: Determination of cefdinir in laboratory prepared mixtures with its acid and alkaline degradation products by the proposed HPTLC method.

Degradation products µg/mL	Cefdinir µg/mL	% Recovery* of cefdinir in presence of Acid degradation products	% Recovery* of cefdinir in presence of alkaline degradation products
0.5	2	99.44	99.32
1	2	101.91	98.65
2	2	100.26	100.66
Mean ±RSD%		100.54±1.258	99.54±1.023

*Mean of three determinations

Table. 4: Determination of cefdinir in pharmaceutical formulations and application of standard addition technique.

Pharmaceutical formulation	¹D 313.4 nm	²D 298.2 nm	¹DD 312 nm	¹DD 310.2 nm	Mean centering of ratio spectra 288.4 nm	Mean centering of ratio spectra 284.8 nm	HPTLC
Cefdin Capsules 300mg BN: A200707	99.15±0.512	99.91±0.377	99.16±0.306	99.18±0.282	98.71±0.472	99.34±0.936	100.14±1.763
Standard addition technique (mean±RSD%)	99.63±0.994	99.96±0.778	99.80±0.981	99.65±0.740	100.12±0.923	100.08±0.682	100.48±0.900
Cefdin suspension 125mg/5mL BN: N100431	101.13±0.387	100.44±0.338	101.61±0.681	100.22±0.411	100.02±0.420	100.96±0.249	99.74±1.792
Standard addition technique (mean±RSD%)	100.07±0.838	99.91±0.418	100.26±0.780	99.43±0.535	100.22±0.479	101.01±0.816	100.43±1.156
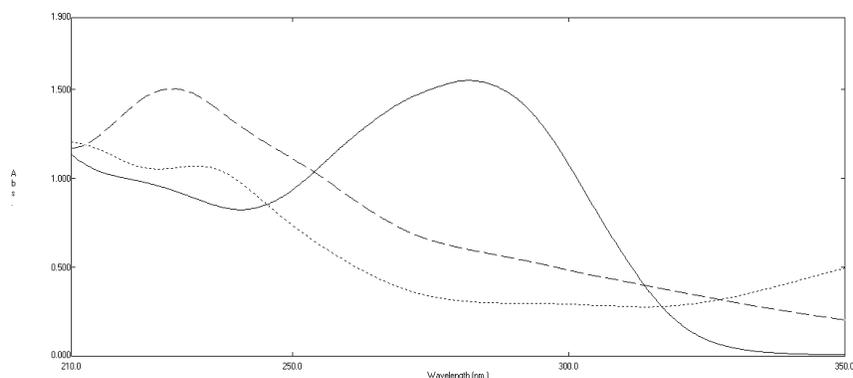
Fig. 1:   Zero order absorption spectra of CFD (—), its acid (- -) and alkaline degradation products (…) (24.00 µg/mL each).
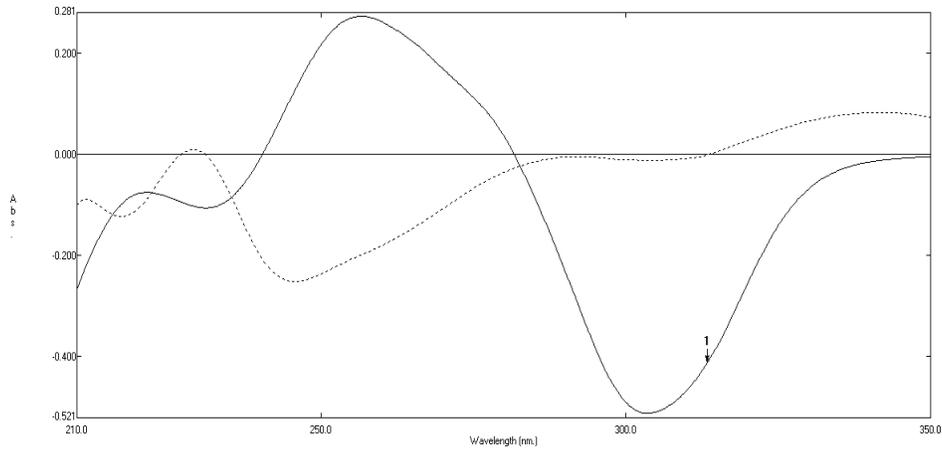
Fig. 2:   First derivative (^{1}D) absorption spectra of CFD (—) and its alkaline degradation products (…) (24.00 µg/mL each).
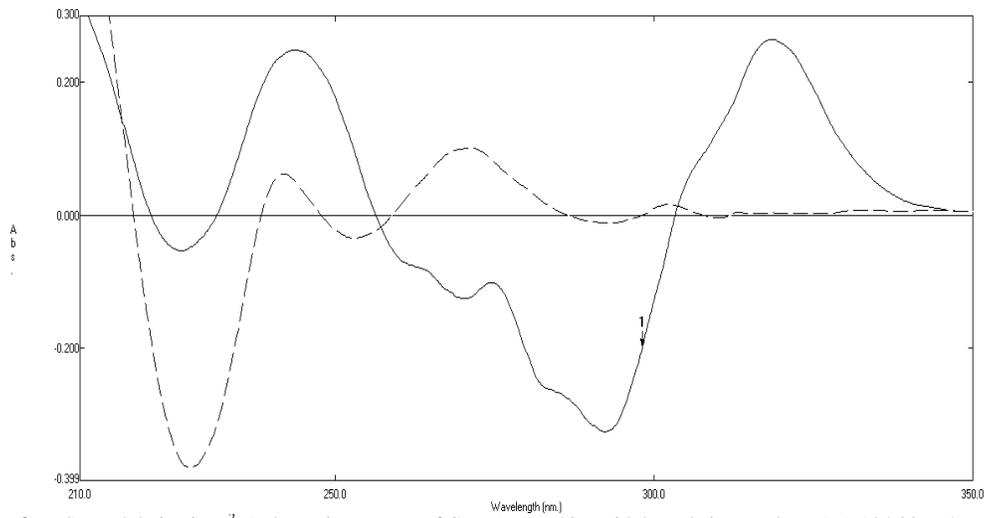
Fig. 3:   Second derivative (^{2}D) absorption spectra of CFD (—) and its acid degradation products (- -) (24.00 µg/mL each).
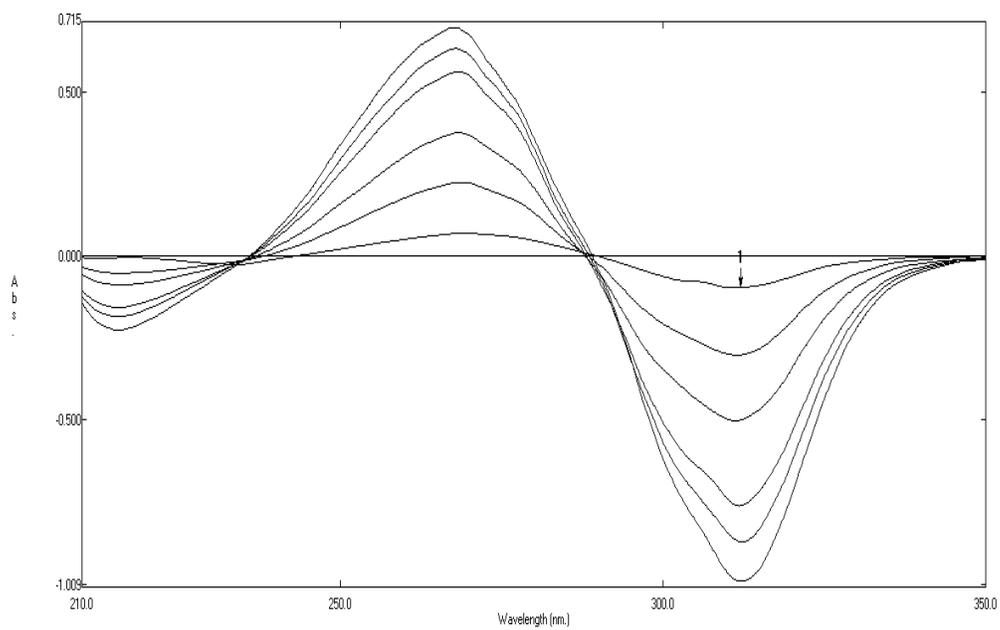
Fig. 4: First derivative of ratio spectra (^{1}DD) for different concentrations (2.00 -30.00 µg/mL) of CFD at 312 nm using acid degradation products (40.00 µg/mL) as divisor.
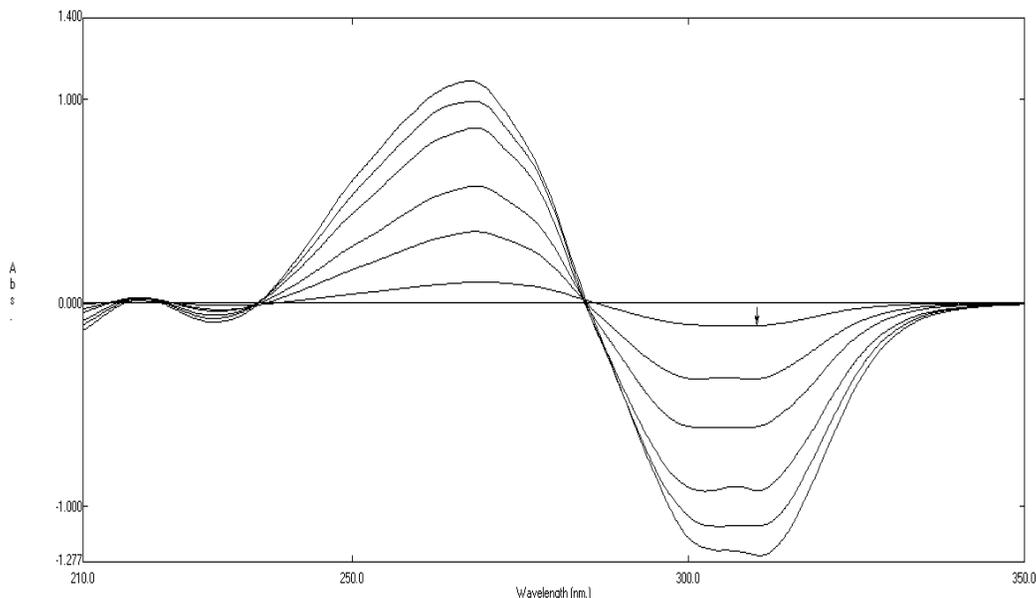
Fig. 5: First derivative of ratio spectra (^{1}DD) for different concentrations (2.00 -30.00 µg/mL) of CFD at 310.2 nm using alkaline degradation products (40.00 µg/mL) as divisor.
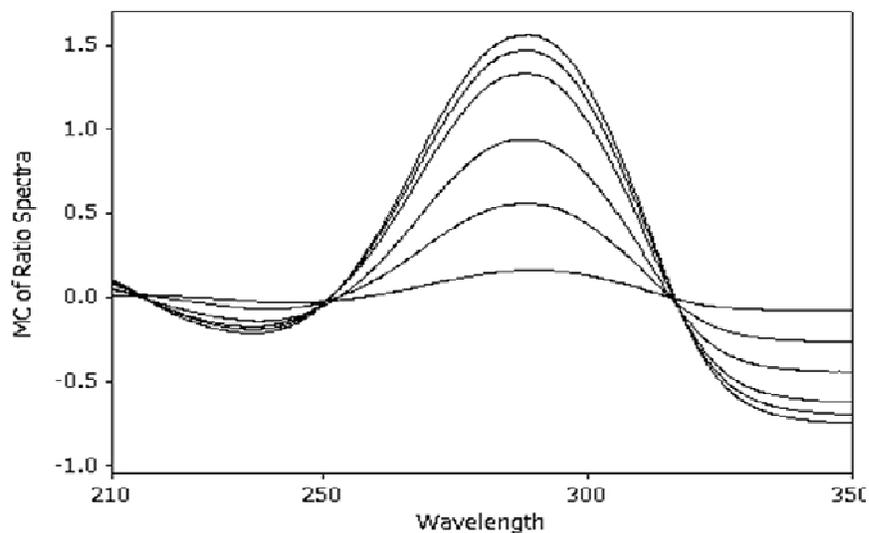
Fig. 6: Mean centering of ratio spectra for different concentrations (2.00 -24.00 µg/mL) of CFD at 288.4 nm using acid degradation products (40.00 µg/mL) as divisor.
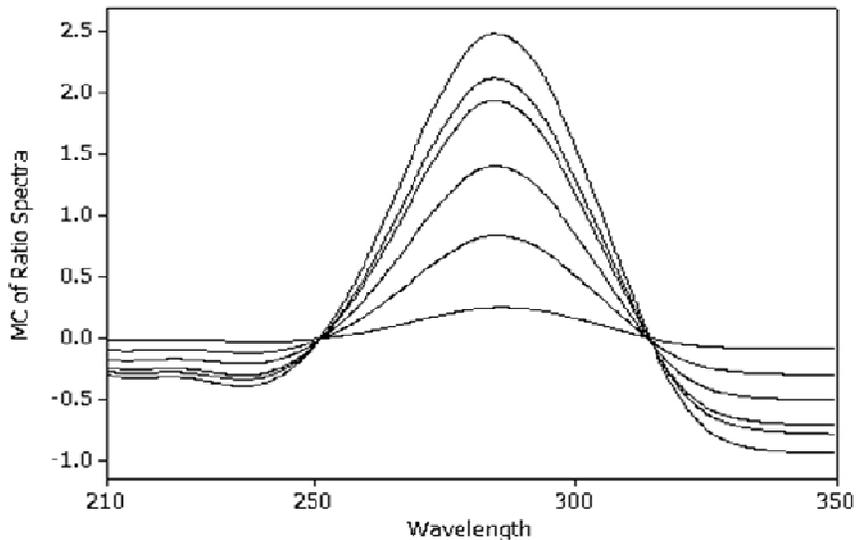
Fig. 7: Mean centering of ratio spectra for different concentrations (2.00 -26.00 µg/mL) of CFD at 284.8 nm using alkaline degradation products (40.00 µg/mL) as divisor
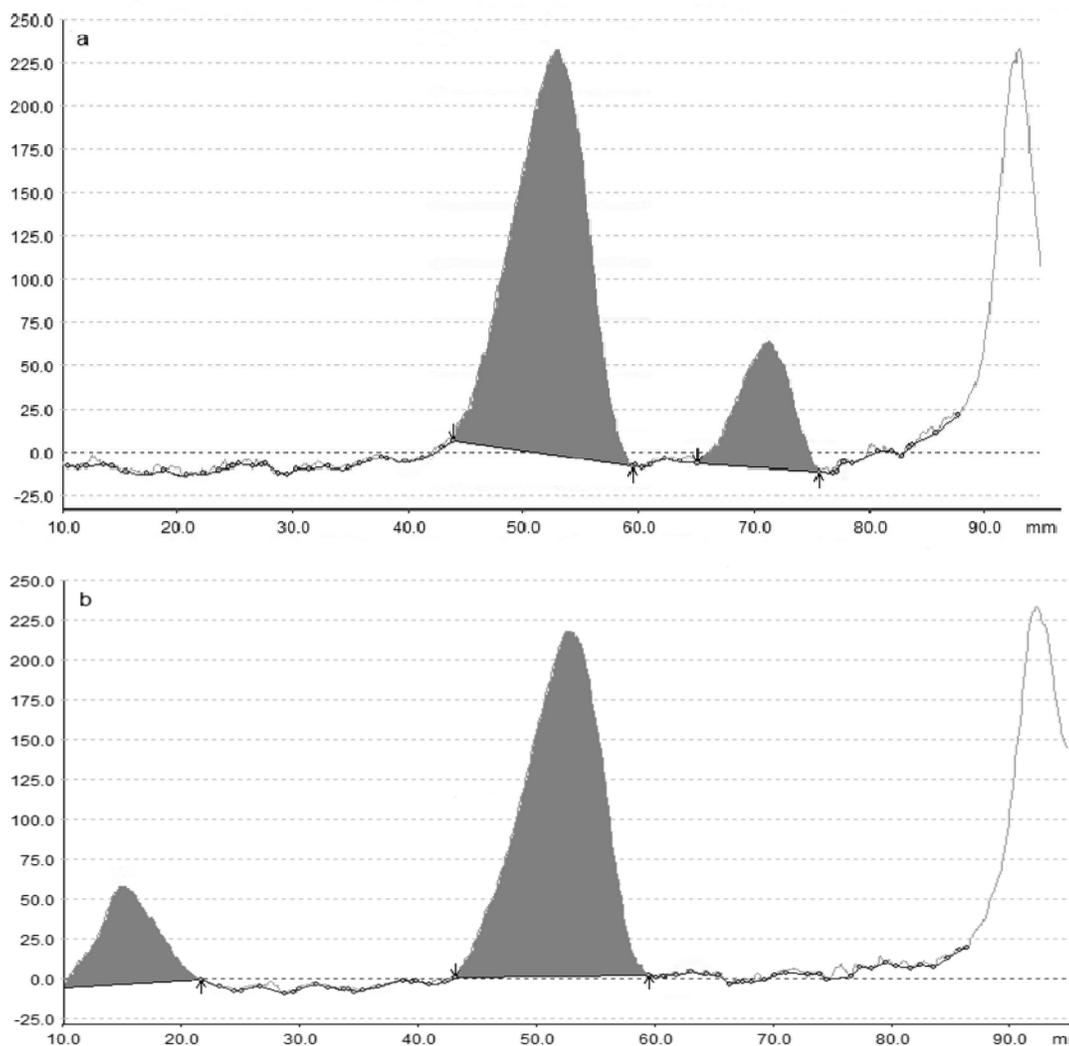
Fig. 8: HPTLC chromatograms of mixture solutions containing CFD 2.00 µg/spot with its acid (a) and alkaline-(b) degradation products (1.00 µg/spot each).

HPTLC-densitometric method

　　For HPTLC, experimental conditions such as developing system and wavelength of detection were optimized to provide accurate, precise and reproducible results. Different developing systems were tried such as diethylether: methanol (7.0: 3.0, v/v). This developing system gave poor resolution between the intact drug and its acid degradation product. Thus, the polarity of this system was changed by adding different volumes of water and glacial acetic acid. The best resolution with minimum tailing of CFD peak from its hydrolytic degradation products was achieved by using diethylether-methanol-water-glacial acetic acid (6: 3: 1: 0.05, v/v). The separated drug spots were determined densitometrically on the plates at 285 nm. The tailing factor of CFD peak was 1.4 and R_f values were 0.50 for CFD and 0.71 and 0.05 for its acid and alkaline degradation products, respectively (Figures 8a and 8b). For quantitative application using HPTLC, the calibration curves are generally inherently non-linear due to scattering of light.   They generally comprise a pseudo-linear region at low sample concentration and then departure from linearity begins at higher sample concentrations (Poole and Poole,

1989). Moreover, the ICH guidelines mentioned that for some analytical procedures which do not demonstrate linearity, the analytical response should be described by an appropriate function of the concentration of an analyte sample.

　　The relationship between the integrated peak area and the concentration was evaluated with linear and polynomial regression functions. Fitting with linear function gave correlation value, r = 0.9864 while fitting with polynomial function gave better correlation (r = 0.9995) and lower standard deviation values and was therefore used for quantitative analysis. Calibration curve was constructed in the range of 0.50-6.00 µg/spot.

　　Assay validation parameters for HPTLC method are presented in Table 1. The specificity of this method is illustrated in Figure 6 where complete separation of CFD from its acid and alkaline degradation products was noticed, and also tested by analyzing the laboratory prepared mixtures.

　　The results are presented in Table 3. From the data obtained, one can conclude that CFD can be determined without any interference from its different hydrolytic degradation products. CFD containing dosage forms were analyzed by the

proposed spectrophotometric and HPTLC methods and satisfactory results were obtained and were in a good agreement with the label claims (Table 4). Standard addition technique was also applied and the results obtained are shown in Table 4. The results of analysis of the pharmaceutical formulation and the standard addition method suggest that there is no interference from any excipients.

CONCLUSION

The proposed spectrophotometric and HPTLC methods are simple, rapid, accurate, precise and specific over the specified ranges. The proposed methods are considered as stability indicating methods for the determination of CFD in presence of its acid and alkaline induced hydrolytic degradation products without prior extraction. Hence, these methods are suitable for stability testing of CFD and for routine quality control analysis in bulk material and in pharmaceutical formulations where economy and time are essential.

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